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Methylation Age In MPN Patients As A Correlate For Disease Status, Allele Burden And Therapeutic Response

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1 Abstract

1 ePoster

Suzanne McPherson

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METHYLATION AGE IN MPN PATIENTS AS A CORRELATE FOR DISEASE STATUS, ALLELE BURDEN AND THERAPEUTIC RESPONSE

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All contributions

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Abstract: P697

Type: Poster Presentation

Presentation during EHA22: On Saturday, June 24, 2017 from 17:30 - 19:00

Location: Poster area (Hall 7)

Background

Myeloproliferative Neoplasms (MPNs) result from genetic and epigenetic dysregulation. Epigenetic therapies, such as Vorinostat (SAHA, MK-0683), a histone deacetylase inhibitor, have been tested as a therapeutic strategy in these patients. Examining the epigenetic landscape in MPN may provide new insights into predicting therapeutic response and therefore enhance the clinical utility of these agents. Probably the best described epigenetic mechanism is DNA methylation (DNAm); in which methyl groups are added to DNA at CpG sites regulating chromatin compaction and gene expression/repression. DNAm is known to be altered by ageing and can reflect the effect of diet, lifestyle or disease on cellular processes. Therefore 'methylation age' (MA) may be a more accurate reflection of disease than 'chronological age' (CA), which is merely a description of how long a person has been alive. Weidner *et al* (*Genome Biology*, 2014) described how the measurement of DNAm levels at CpGs within 3 genes, *ASPA*, *ITGA2B*, *PDE4C* enabled the determination of a reliable MA that reflected CA in normal individuals.

Aims

The aim of our study was correlate MA with disease status, mutational profile and therapeutic response in a cohort of MPN patients treated with Vorinostat.

Methods

MA was calculated following pyrosequencing of bisulfite converted DNA from 40 MPN patients on an investigator initiated non randomised open label phase II multicentre study of Vorinostat (EudraCT #2007-005306-49). Paired samples were analysed at trial entry and after 3 months of therapy to calculate their individual MA scores. Validation of methods used and ageing signature calculation was carried out using cell line and healthy volunteer material.

Results

Samples from 18 Essential Thrombocythaemia (ET) and 22 Polycythaemia Vera (PV) patients (23 F/17 M) with a mean age of 62 years (range 29-81) were assessed. *JAK2V617F* was detected in 77.5% (n=31/40). Complete clinical response (CR) was achieved in 8 patients, partial (PR) in 17, and no response (NR) in 15 patients. MA was on average 8.3 years younger than CA (range -43.4 to +41.6) at time of trial entry and 8.2 years younger (range -36.5 to +33.3) after therapy. This difference between MA and CA was greater in ET patients compared to PV, both at trial entry (-14.0 years vs -3.7) and after therapy (-13.0 years vs -4.3). A statistically significant link between *JAK2* allele burden and MA was seen: compared to patients with low or no *JAK2* allele burden, patients with high *JAK2* (>60% at baseline) had an older MA at trial entry (64.2 years vs 44.5, p=0.0007) and after therapy (64.3 years vs 44.6, p=0.0015). This difference was also seen when PV or ET patients were examined separately. Patients with a high *JAK2* allele burden tended to have a MA closer to their CA at trial entry (-0.6 years vs -15.3, p=0.0122) and after 3 months therapy (-0.5 years vs -15.2, p=0.0072).

Although the cohort size was small, within the ET group, NR compared to PR was associated with a younger MA after therapy (41.4 years vs 56.3, p=0.0156). Within PV, NR compared to PR was associated with a MA that was older than CA both before (+9.2 years vs -14.2 years, p=0.0346) and after therapy (+7.4 years vs -13.9, p=0.0347).

Conclusion

This study suggests a link between MA and *JAK2* mutant allele burden in MPN patients, suggesting that allele burden not only has a role in clinical phenotype and disease evolution but in the overall methylation landscape of the mutated cells. However, the role of MA with respect to therapeutic response needs to be clarified with further studies required to show its full impact.

Session topic: 15. Myeloproliferative neoplasms - Biology

Keyword(s): Myeloproliferative disorder, Methylation, histone deacetylase inhibitor, Epigenetic

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